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Applicant: MORINAGA MILK INDUSTRY CO., LTD., 33-1, Shiba 5-chome, Minato-ku, Tokyo 108 (JP)

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(2) Inventor: Okonogi, Shigeo, 10-12, Chuo 5-chome, Ohta-ku Tokyo (JP)
Inventor: Tomita, Mamoru, 47-6, Higashi
Asahina 1-chome Kenazawa-ku, Yokohama City
Kanagawa Prefecture (JP)
Inventor: Shimamura, Seilchi, 1558 Shinoharamachi
Kohoku-ku, Yokohama City Kanagawa Prefecture (JP)
Inventor: Ishihara, Norlo, 3-21, Shinmei Minami 2-chome,
Adachi-ku Tokyo (JP)
Inventor: Kudo, Tsutomu, 4-74, Wakakusadai Midori-ku,
Yokohama City Kanagawa Prefecture (JP)

Representative: Quest, Barry et al, M'CAW &

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Representative: Quest, Barry et al, M'CAW & CO. 41-51 Royal Exchange Cross Street, Manchester M2 7BD (GB)

(54) Granular product of dried microorganism cells and manufacturing method therefor.

Granular product prepared by fluidizing core material such as succharide in a granulating chamber, spraying melted binding material such as fat to said fluidized core material and concurrently feeding dried viable microorganism cells such as bifidobacterium towards said fluidized core material to form granular product of stratified structure by adhering said microorganism cells on periphery of said core material. Since the product is prevented from permeation of atmospheric oxygen and environmental moisture, cells survival rate of the product is higher than that of the conventional product during prolonged storage period.

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GRANULAR PRODUCT OF DRIED MICROORGANISM CELLS AND MANUFACTURING METHOD THEREFOR

TECHNICAL FIELD OF THE INVENTION

The invention relates to a granular product of stratified structure having higher viability for prolonged storage prepared from dried viable microorganism cells and a method for manufacturing thereof.

BACKGROUND AND PRIOR ART

It has been well known for a long time that oral administration of some viable bacteria or lactic acid bacteria to human beings and animals improve intestinal function and widely practiced to orally administrate such viable microorganism for maintenance and promotion of health, for instance by adding these microorganism to foodstuffs or feedstuffs. The various kind of microorganisms are used for that purpose and various kind of products containing thereof are known, for instance powder, granule, gel, liquid and so on. Recently medical preparations, foodstuffs and feedstuffs containing with lactic acid bacteria or bifidobacteria have held public attention.

It is, however, very difficult to preserve such product containing viable microorganism cells for a long time without decreasing cell survival rate. Because the viability of these bacteria in this product is considered to decrease when environmental conditions are changed during storage. However, when such microorganism cells are preserved under the

condition of lowered environmental moisture microorganism cells turn to resting cells and it is possible to storage the microorganism cells for a long period.

Thus, cultivated and collected microorganism cells have hitherto been washed, added with a cryoprotectant, freeze-dried or vacuum-dried, pulverized, sifted out, added with starch or lactose as excipient and added with sugar or acidulant to obtain powdered product. Such powdered products are often reprocessed after addition of suitable substances into granular or other block-type product. In the conventional method, it is important to keep moisture content of the product as low as possible during the whole processing steps. However, it is not always easy to strictly keep such condition. Resting cells of microorganism are activated by addition of water to dried microorganism cells in step of processing or absorption of atmospheric moisture by the dried product for period of storage. case, however, as the condition of survival for microorganism cells is extremely unsuitable, it is impossible to achieve sufficient viability of

It has been known that viability of the product containing dried microorganism cells during storage period is effected by the presence of atmospheric oxygen, since free radicals are induced therein.

microorganism cells.

Therefore, it has been disclosed to suspend such dried viable microorganism cells in oil or fat for preventing from permeation of environmental moisture (Japanese Unexamined Patent Application Gazette 2908/1981), to coat powder containing dried viable

- bifidobacteria with fat or oil for preventing from permeation of environmental moisture, and atmospheric oxygen (Japanese Unexamined Patent Application Gazette 33543/1982) and to pelletize mixture of powder
- s containing dried viable bifidobacteria with oil or fat for preventing from permeation of environmental moisture and atmospheric oxygen which is used as a material to prepare various confections (Japanese Unexamined Patent Application Gazette 32221/1982).

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According to above prior arts, however, dried viable microorganism cells are only mixed with fat or oil or only suspended in fat or oil. Thus powder particles in prior arts are not always completely coated with fat or oil and consequently the products 15 prepared by the above prior method do not achieve sufficient viability.

Futhermore, it has also been in public knowledge to mix dried viable bifidobacteria with sufficiently dried starch in order to extremely decrease water z content thereof to prepare pelletized confections (Japanese Unexamined Patent Application Gazette 4976/1984). According to said prior art, however, it might be possible to decrease water content in the product just after manufacturing thereof but it is almost impossible to keep the product preventing from permeation of environmental moisture and atmospheric oxygen as it is. The product must be contained in a hermetically sealed container in which air is replaced with nitrogen. It goes without saying that such additional step and cost of additional material will occupy a considerable portion of the whole cost of the product.

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The inventors have tried to overcome or improve the defects of the prior arts in this technical field to find out a way for granulating dried viable microorganism cells without using any water and granule of thus prepared product having stratified structure like as onion and excellent viability, on which this invention is based.

BRIEF EXPLANATION OF THE INVENTION

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It is, thus, an object of the invention to provide granular product containing dried viable microorganism cells, which prevents from permeation of environmental moisture and atmospheric oxygen.

The other object is to provide granular product containing dried viable microorganism cells which have excellent viability during a prolonged storage period.

The still other object is to provide a method for preparing granular product containing dried viable microorganism cells by granulating without using any water which has excellent viability during a prolonged storage period.

Said objects and various advantages to be appreciated by studying the specification may be attained by a granular product containing dried viable microorganism cells characterized by consisting of at least 0.1% by weight of a core material and less than 99.9% by weight of an adherent composition which comprises at least 5% by weight of a binding material substantially containing no water having a melting point of 25° to 60°C and less than 95% by weight of dried viable microorganism cells, and having a

stratified structure of said adherent composition surrounding said core material, on the one hand; and the other hand by the process for manufacturing granular product containing dried viable microorganism cells characterized by fluidizing core material in a granulating chamber, spraying melted binding material which contains substantially no water and concurrently feeding dried viable microorganism cells towards said fluidized core material to form granular product of stratified structure by adhereing said microorganism cells on periphery of said core material.

DETAILED EXPLANATION OF THE INVENTION

The granular product according to the invention consists of a core material and an adherent material containing dried viable microorganism cells and binding material for coating said core material with said adherent material in stratified structure.

As the core material, crystaline granullated sugar, sugar/starch composition, particles prepared pelletizing said materials, saccharide such as sucrose lactose and glucose, acid crystales such as tartaric acid and citric acid, mixture thereof, particles prepared by pelletizing thereof, and any other materials may be used so far as they are edible and have hardness and size suitable as core of the nature referred to above. For instance dried viable microorganism cells itself, pelletized product of such powder mixed with sugar or other additive prepared according to the prior art, and even granular product prepared according to the invention may be used as the

 core material of the invention. The water content of core material is preferably as low as possible, less than 5 weight %.

The core material may be used in the amount

ranging from 0.1 weight % relative to the product up
to such a considerably large amount that dried powder
of microorganism is coated in a thin layer around the
core, but from the practical view point it preferably
ranges from 1 to 80 weight %.

- As the binding material, fat and oil, lipid, emulsifier, glyceride, sorbitan fatty acid ester, propylene glycol fatty acid ester, sucrose fatty acid ester, paraffin, wax and any other materials or any mixture thereof may be used so far as it is edible and capable of exhibiting adhesion in the course of solidification of the melted binding material. It is necessary, however, that the binding material has a melting point ranging from 25°C to 60°C. When the binding material having a melting point higher than 60°C, the granulating chamber will have to be kept at
- ²⁰ 60°C, the granulating chamber will have to be kept at a temperature above 55°C, at which microorganisms are partly killed and partly so damaged as to be killed later. On the other hand, if the melting point of the binder is lower than 25°C, formed granules are apt to be agglomerated.

The amount of the binding material to be used in the invention is more than 5 weight %, and preferably ranges from 10 to 50 weight % based on the adherent material. When the amount is less than 5 weight %, sufficient adhesion cannot be attained so that desired granules are not formed or formed granules are easily collapsed due to lower hardness.

The strain of microorganism used in this invention is decided depending on the use of the granular product or the purpose for manufacturing said product according to the invention. If it is intended to manufacture the granular product having improved intesinal function, known lactic acid bacteria belonging to the genus Lactobacillus, Leuconostoc and Streptococcus, and known bacteria belonging to the genus Bifidobacterium are preferably used. One or more bacteria which are normally found in the human or the animal intestinal tract are sometimes preferably added thereto. When manufacturing the granular product for production of silage, Streptococcus faecalis or Lactobacillus plantarum is preferably 15 used.

The cultivated bacteria as referred to above are subjected to freeze-drying or vacuum drying according to the usual method. The obtained dried material may be crushred, sifted out and may be directly used for granulation, but powdered mixture which is added with lactose, starch and other additives as excipient preferably used. It is possible to control the number of viable microorganism cells in the powdered mixture by adjusting the amount of excipient to be added. The particle size of the powdered mixture is preferably below 100 mesh, and more preferably below 150 mesh.

The granular product prepared by the invention is concentric circles in section so as to form multilayers of adherent material by adhereing it around the core material. The outer surface of the granule may be coated with a desired material such as sugar, which is also one embodiment of the invention.

Characteristic features of the manufacturing process according to the invention are as follows. The adherent material in the amount of less than 99.9 weight % which comprises a binding material having 25° 5 - 60°C of melting point substantially containing no water and dried viable microorganism cells is adhered to a fluidized core material of at least 0.1 weight % to form granular product of stratified structure. binding material of at least 5 weight % as one 10 component of the adherent material is sprayed to said fluidized core material and concurrently dried viable microorganism cells of less than 95 weight % as the other component of the adherent material feeded The temperature of granulating chamber is thereto. B adjusted depending on the properties of said binding material so that dried viable microorganism cells are adhered on the surface of core material by and by in layers until reaching the desired size owing to adhesion of melted binding material to be gradually 20 solidified.

In the process of the invention, thus, it is important to relevantly control the conditions of (1) fluidizing of the core, and (2) feeding temperature of the binding material and temperature of the granulating chamber.

(1) Fluidizing;

It is necessary that the core material moves at a relevant fluidizing rate and suitable rotating rate in the granulating chamber so that dried viable microoragnism cells may be uniformly adhered the fluidizing core material without loss of adherent

material by and by so as to form smooth spheres of stratified structure.

In order to realize such fludizing condition, centrifugally fluidizing method is preferably used.

The apparatus for carrying out said method comprises a chamber having a plurality of slits for blowing air formed in the bottom of peripheral wall which is mounted for rotation at the bottom of a granulating chamber so that core material and granulating particle coated with the adherent material are fludized around the periphery of the chamber respectively with rotating by virtue of centrifugal force caused by the rotation of the chamber with aid of agitating force by air blown through said slits.

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(2) Feeding temperature of the binding material and temperature of the granulating chamber;

The melted binding material is fed through a conduit by means of a pump respectively heated so as to keep the binding material at a relevant temperature and in the melted state towards fludizing core material respectively with rotating in the granulating chamber kept at a suitable temperature. When said temperature is too low, the binding material is solidified so fast that adhesive function of the binding material is not exhibited and consequently desired granules can not be obtained. On the other hand, when said temperatures are too high, the binding material can not be solidified or too late solidified, relevant adhesiveness is not available so that desired granulation can not be attained. In addition thereto microorganism cells contacted with too hot binding

material is partly killed.

From the above, the feeding temperature of the binding material is preferably kept at the range of 35° to 75°C which is 10° to 15°C higher than the melting point of the binding material. The temperature in the granulating chamber is preferably kept at the range of 15° - 55°C which is 5° to 10°C lower than the melting point of the binding material.

Control of the temperature in the granulating chamber may be carried out by adjusting temperature of air blown out through the slits formed in the peripheral wall of the chamber.

It is possible to carry out further coating of desired material on the surface of granular product according to the just same method. Such coating is made for the purposes of preventing from permeation of environmental mositure and atmospheric oxygen, giving palatable taste, flavor and color and enteric coating. For example, the coating for preventing from

- permeation of environmental moisture and atmospheric oxygen is carried out by using only binding material according to the present method. In order to enteric coating, shellac or zein is coated on the surface of granular product by means of the same granulating
- apparatus. According to such coating the granular product of the invention is widely used for various purposes. It is also possible to combine vitamines, growth factors of intestinal flora, health foods with said core material, dried viable microorganism cells
- 30 and binding material.

Some embodiments of the invention shall be given in reference to following experiments and examples for the purpose of explaining the invention more definitely but not for limiting the scope of the invention thereto, which should be decided only by Claims given thereafter with taking into consideration of the spirits to be appreciated by studying the specification throughout.

Experiment 1 (Survival rate of microorganism
cells in the granular product)

Survival rates of microorganism cells in the granular products according to the invention without using any water in the granulating process and according to the conventional method where water or aqueous solution was used therefor were determined as follows.

- (a) Granular product of the invention (Sample No 1);
- This was prepared in the same manner as shown in Example 1.
- (b) Granular product of control 1 (Sample No. 2)

 This was prepared in the same manner as shown in

 Example 1, but as the binding material 50% aqueous

 solution of sucrose was used instead of palmitic acid

 propylenglycol ester of m.p. 35°C. Obtaining granular

 product was dried and its moisture content was less

 than 4 weight %.
 - (c) Granular product of control 2 (Sample No. 3);
 This was prepared as follows.

Dried viable bifidobacteria cells 20 weight % used in Example 1

Corn starch	50	Ħ
Dried skim milk	10	ĸ
Aqueous solution of 50% sucrose	20	•

Pasty mixture obtained by blending the above components was granulated by means of conventional screen extruder. The obtained granular product was dried and its moisture content was less than 4 weight %.

(d) Determination of cell survival rates;

As to said three samples, the viable count of bifidobacteria in powder before granulation and in the granular product after granulation of said powder was determined according to the method of Mitsuoka et al using BL agar culture medium ("Nihon Saikingaku Zasshi" (Japanese Journal of Bacteriology) Vol.33, No.6, Page 753 (1978)). Cell survival rates were calculated by using following equation (I).

Cell survival rate(%) = viable count of granular product x 100/(Viable count of powder x % of dried viable microorganism cells in the product/100) ... (I) The results of this test are shown in Table 1.

Table 1 Cell survival rate

25	Sample No.	Sample	Survival rate(%)
	1	Granular Product of Invention	93
30	2	Control 1	. 1.3
au	3	Control 2	2.9

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As will be seen from Table 1, it is definitely clear that the cell survival rate of the granular product of the invention in which granulation is carried out without using any water is remarkably higher than that of the products prepared by the prior arts with using water or aqueous solution.

Experiment 2 (Viability of the granular product)

The effects of atmospheric oxygen and environmental

moisture on survival rates of bifidobacteria in the
granular products prepared by the method of present
invention and prior arts were tested as follows.

- (a) Granular product of the invention (Sample No. 1);
- This was prepared in the same manner as shown in Example 1.
 - (b) Granular product of control 1 (Sampel No. 2); This was prepared as follows.
- Dried viable bifidobacteria cells
 used in Example 1

 Lactose

 Vegetable oil and fat(m.p. 39°C)

 50 weight %

 15 "

 35 "
- Pastry mixture obtained by blending the above components was granulated by means of conventional screen extruder.
- (c) Tablet of control 2 (Sample No. 3);
 This was prepared as follows.

Dried viable bifidobacteria cells 10 weight % used in Example 1

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Lactose (added for pelletizing)	25	n
Dried corn starch	5	. 11
Powdered sugar	40	
Dried skim milk	18	×
Lubricant	2	ū

The mixture of the above components was formed to tablet by means of conventional tableting machine.

(d) Effect of atmospheric oxygen;

Each of said samples Nos. 1, 2 and 3 was put into two hermetically sealed containers, one of which was filled with nitrogen gas replaced with air (oxygen absence) while the other as it was (oxygen presence). Totally six (6) containers were kept in an incubator at 37°C for one month.

The viable count of bifidobacteria in the granular products before and after storage was determined by the same manner as in Experiment 1.

Cell survival rate of each samples was calculated by following equation (II).

Cell survival rate(%) = (Viable count of the sample

Cell survival rate(%) = (Viable count of the sample after storage/Viable count of the sample before storage) x 100(II)
The results of this test are shown in Table 2.

Table 2
Effect of Atmospheric oxygen on cell

)	Sample No.	Sample	Gas in container	Survival Rate (%)
	1	Invention	Air	57
			Nitrogen	60

25

2	- 15 - Control 1 Air Nitrogen	32 58
3	Control 2 Air Nitrogen	29 59

As will be appearent from Table 2, there is no essential difference in the survival rates between the products of the invention which were preserved, in the presence and absence of oxygen. In contrast therewith, it is obviously recognized that the survival rates of Controls 1 and 2 were considerably affected with atmospheric oxygen. This means that the viable counts of bifidobacteria in these samples decreased extremely during a storage. The granular product of the invention can be packed without replacing air in the container with nitrogen, which makes it possible to considerably lower the cost of the packed product according to the invention.

(e) Effect of environmental moisture;

Each of said Sample Nos. 1, 2 and 3 was put on a petri dish without cover and equilibrated with saturated solution of potassium carbonate in desiccator for one month at a temperature of 37°C and 43% of relative humidity.

The viable count of bifidobacteria in each of the samples before and after storage was determined by the same manner as in Experiment 1. Cell survival rate of each sample was calculated by above equation (II).

me The results of this test are shown in Table 3.

- 16 - Effect of evironmental moisture on cell

Sample No.	Sample	Survival Rate (%)
1	Invention	24.1
2	Control 1	8.3
3	Control 2	1.5

As will be seen from Table 3, the granular product of the invention shows excellent property for preventing from permeation of atmospheric moisture in the severe storage conditions in comparison with the products of the prior art. On the other hand, the granules of the Controls 1 and 2 were highly hygroscopic, changed to brownish color in appearance and decreased hardness during a storage. Therefore, the granular products prepared by the prior arts can not be preserved for a long period of storage.

Example 1

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Three hundred grams of finely granulated sucrose

(Trade name "NONPARREL 101" by Freund Sangyo Co., Ltd)

of 14 - 20 mesh in particle size as the core material

was put into granulating chamber of the centrifugal
fluidizing granulator (Type CF-360 by Freund Sangyo

Co., Ltd). By rotating the chamber and blowing air of

27° - 30°C from the slits formed in the peripheral

wall, said fluidized core material was formed and the
temperature of said chamber was kept at 27° - 30°C.

Three hundred milliliters of propyleneglycol palmitic acid ester (m.p. 35°C) as binding material was kept at about 50°C and sprayed at a rate of 20 ml/min towards said fluidized core material.

- S Concurrently 1 kg of dried viable bifidobacteria (Bifidobacterium longum ATCC 15708) cells (The viable count bifidobacteria, 1.0 x 10¹⁰/g) was fed through a screw-feeder to said fluidized core material for 15 minutes.
- Thus, 1.5 kg granular product containing bifidobacteria was obtained, in which mean particle diameter was about 1.7 mm and mean particle weight was about 3.5 mg. The content of dried viable bifidobacteria in the granular product was was 63.7% by weight and viable count of bifidobacteria was 59 x 10⁸/g. The cell survival rate calculated from above equation (I) was about 93%.

Example 2

Five hundred gram of the granular product

prepared by the same manner as in Example 1 was

fluidized according to the centrifugal fluidizing

granulator as in Example 1, under the controlled

temperature at 30° - 32°C in the granulating chamber.

Three hundred milliliters of 5% (W/V) ethanolic

solution of shellac was sprayed towards said fluidized

granular product at a rate of 10 ml/min to coat said

granular product with shellac. Then 500 ml of 5%

(W/V) ethanolic solution of zein was sprayed towards

said fluidized granular product at a rate of 10 ml/min.

Then the product was dried in vacuum at 30°C for 6

hours to obtain granular product coated with shellac

and zein. About 520 g of final product having 7.4% by weight of the coating material and 48 x 10⁸/g in viable count of bifidobacteria was obtained. The cell survival rate calculated by following equation was about 88%.

Cell survival rate(%) = (Viable count of sample after coating/Viable count of sample before coating) x 100.

Example 3

- Three hundred grams of finely granulated sucrose (same substance to Example 1) of 20 to 24 mesh in particle size as a core material was put into the granulating chamber as in Example 1. Said core material was fluidized by blowing air from the slits 15 with controlling volume and temperature thereof, and the temperature in said chamber was kept at 32° - 35°C. Five hundred milliliters of vegitable fat (m.p. 42°C) kept at a temperature of about 55°C was sprayed towards said fluidized core material at a rate of 20 ml/min. Concurrently 1 kg of dried viable lactic acid bacteria (Streptococcus faecalis ATTCC 8043) cells (viable count of said bacteria; 25 x 108/q) was fed through the screw feeder to said fluidized core material for about 25 minutes.
- About 1.7 kg of granular product having about 1.5 mm in mean particle diameter and about 2.9 mg of mean particle weight was obtained. The final product contained 57.1% by weight of dried lactic acid bateria cells.
- The viable count of said bacteria in the final product was determined by the method for testing of viable count of lactic acid bacteria ("Standard

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Methods of Analysis for Hygienic Chemists - With Commentary", page 257, Edited by Pharmaceutical Society of Japan, Published by Kinbara Publishing Co., Ltd.,(1980)) to be 14 x 10⁸/g. The cell survival rate calculated frour above equation (I) was about 98%.

· What is claimed is;

- 1. A granular product containing dried viable microorganism cells characterized by consisting of at least 0.1% by weight of a core material and less than 99.9% by weight of an adherent composition which comprises at least 5% by weight of a binding material substantially containing no water having a melting point of 25° to 60°C and less than 95% by weight of dried viable microorganism cells, and having a stratified structure of said adherent composition surrounding said core material.
- A granular product according to Claim 1,
 wherein said granular product is further coated with at least one coating agent selected from the group consisting of agent preventing from permeation of atmospheric oxygen, agent preventing from permeation of environmental moisture and enteric coating agent.
 - A granular product according to Claim 1, wherein said coating agent is shellac or zein.
- 4. A granular product according to Claim 1,
 wherein said core material is a substance selected
 from the group consisting of saccharide, dried viable
 microorganism cells, graules containing dried viable
 microorganism cells as main content, capsules
 containing dried viable microorganims cells as main
 content and mixture thereof.
 - 5. A granular product according to Claim 1,

wherein said binding material is a substance selected from the group consisting of natural fat and oil, synthetic glyceride, emulsifier, parafin, wax and mixture thereof.

6. A process for manufacturing granular product containing dried viable microorganism cells characterized by fluidizing core material in a granulating chamber, spraying melted binding material which contains substantially no water and concurrently feeding dried viable microorganism cells towards said fluidized core material to form granular product of stratified structure by adhereing said microorganism cells on periphery of said core material.

7. A process according t Claim 6, wherein said granular product is coated with coating agent selected from the group consisting of agent preventing from permeation of atmospheric oxygen, agent preventing from permeation of environmental moisture, enteric coating agent and mixture thereof.

- 8. A process according to Claim 7, wherein said coating agent is shellac or zein.
- 9. A process according to Claim 6, wherein fluidization of said core material is carried out by rotating said granular chamber.
- 10. A process according to Claim 6, wherein the amount of said core material is 1 to 80% by weight and the total amount of said microorganism cells and said

 binding material is 20 to 99% by weight in which said microorganism cells and said binding material are 50 to 90% and 10 to 50% by weight respectively.

- 11. A process according to Claim 6, wherein fluidization of core material is carried out at the temperature of 15° to 55°C which is 5° to 10°C lower than the melting point of said binding material.
- 12. A process according to Claim 6, wherein the spray of said binding material is carried out at the temperature of 35° to 75°C which is 10°C higher than the melting point of said binding material.
- 13. A process according to Claim 6, wherein said core material is a substance selected from the group consisting of saccharide, dried viable microorganism cells, granules containing dried viable microorganism cells as main content, tablets containing dried viable microorganism cells as main content, capsules containing dried viable microorganism cells as main content and mixture thereof.
- 14. A process according to Claim 6, wherein said binding material is a substance selected from the group consisting of natural fat and oil, synthetic glyceride, emulsifier, parafin, wax and mixture thereof.

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EUROPEAN SEARCH REPORT

. Application number

EP 85 30 2620

		DERED TO BE RELEVANT		
Category	Citation of document with of releva	Indication, where appropriate, int passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	WO-A-8 201 649	(LARUELLE)	1-5,6- 14	C 12 N 1/04 A 61 K 35/74
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A	BE-A- 667 201 RECHERCHES BIOLO		1,5	
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	The present search report has b	een drawn up for all claims			
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V -	CATEGORY OF CITED DOCU	JMENTS T:	theory or prince earlier patent	L ciple under document,	lying the invention but published on, or plication reasons
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